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Diagnosis and management of early asthma in preschool-aged children

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Asthma is a common disease in young children and is associated with significant morbidity and an increasing prevalence over time. Early childhood wheezing and asthma are heterogeneous disorders; thus identifying phenotypes of asthma remains a goal to identify high-risk children who might benefit from specific therapies or secondary prevention interventions. The typical pattern of illness in preschool-aged children consists of short but recurrent exacerbations of cough and wheeze usually triggered by viral respiratory tract infections. Documenting reversible airflow obstruction on lung function, allergen sensitization, increased IgE levels, or blood eosinophilia is helpful in establishing a diagnosis of asthma in preschool-aged children, if present; however, the diagnosis is most often based on symptom patterns, presence of risk factors, and therapeutic responses. The preschool-aged asthmatic population tends to be characterized as exacerbation prone with relatively limited impairment, unlike older children and adolescents who have more impairment-dominant disease. However, management of persistent disease is based largely on expert opinion and extrapolation from studies in older children given the relative lack of data in this age group. Strategies used to manage intermittent disease include daily and intermittent controller therapy. Management strategies for persistent asthma include daily inhaled corticosteroids, daily leukotriene receptor antagonists, and combination therapies. Finally, regular monitoring of symptom control and medication side effects is important along with titrating controllers to the minimally effective dose. (J Allergy Clin Immunol 2012;■■■:■■■-■■■.)

Key words: *Asthma, wheezing, preschool, inhaled corticosteroids, leukotriene receptor antagonists, intermittent treatment, wheezing phenotypes*

The diagnosis and management of asthma in preschool-aged children differs from that of asthma in school-aged children, adolescents, and adults in a number of ways. The natural history of asthma early in life is quite variable and not fully understood, early childhood wheezing and asthma are heterogeneous disorders with many phenotypic and variable expressions during childhood,[1] and the evaluation of asthma in very young children is further complicated by the lack of objective lung function measurements and definitive biomarkers. Asthma management in preschool-aged children is also complex in that anatomic differences in young children, such as smaller airway size and lower inspiratory flow rate, might affect medication deposition in the airways. Furthermore, it is not clear which therapies are effective for particular wheezing phenotypes or whether early intervention can alter the course and outcome of this chronic disease.

EPIDEMIOLOGY, WHEEZING PHENOTYPES, AND THE SUBSEQUENT RISK OF ASTHMA

In the United States 12.7% of children aged younger than 18 years have been given a diagnosis of asthma at some point in their lifetime (9 million children), and 70% have been reported to have asthma currently (6.5 million).[2] Recently, the US Centers for Disease Control and Prevention has reported that asthma prevalence in children has again increased from 8.7% in 2001 to 9.6% in 2009.[2] Although almost 50% of children report wheeze in the first 6 years of life,[3] only 40% of these toddlers will experience continued wheezing symptoms in later childhood.[3] Identifying phenotypes of pediatric wheezing and asthma and the risk factors associated with each phenotype might help predict long-term outcomes and identify high-risk children who might benefit from secondary prevention interventions.

In the Tucson Children's Respiratory Study, 3 different wheezing phenotypes were identified among 1246 newborns followed for lower respiratory tract infections based on the presence of wheezing symptoms during the first 3 years of life and again at age 6 years.[3] The majority of children (51%) did not experience a wheezing episode. Among those who did have wheezing, the 3 phenotypes identified included the following: (1) early transient wheezers (20%; children with wheezing that began in the first 3 years and resolved by 6 years of age); (2) persistent wheezers (14%; children with wheezing that began before age 3 years

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Abbreviations used
API: Asthma Predictive Index
BHR: Bronchial hyperresponsiveness
EPR3: Expert Panel Report 3
ERS: European Respiratory Society
GERD: Gastroesophageal reflux disease
ICS: Inhaled corticosteroid
LABA: Long-acting β-agonist
LTRA: Leukotriene receptor antagonist
mAPI: Modified Asthma Predictive Index
MDI: Metered-dose inhaler
NAEPP: National Asthma Education and Prevention Program
SABA: Short-acting β-agonist

and was still present at age 6 years); and (3) late-onset wheezers (15%; children who had wheezing between 3 and 6 years of age). Thus, children in the persistent wheezing and late-onset wheezing groups represent those children who are most likely to experience asthma-like symptoms that persist from early childhood into adolescence and adult life, particularly those with atopic features.[4-6] Risk factors associated with persistent wheeze include parental asthma, male sex, atopic dermatitis, peripheral blood eosinophilia at 9 months, early sensitization to food or aeroallergens,[7] lower school-aged lung function, higher levels of airway responsiveness, and a history of wheezing with lower respiratory tract infections.[3] Several of these risk factors have been subsequently confirmed in other cohort studies, with some differences between studies.[8-10]

Terminology, such as episodic (viral) wheeze[11] or severe intermittent wheezing,[12] has been proposed to describe the phenotype for children who primarily wheeze with viral infection alone. In contrast, the term multiple-trigger wheeze has been used for children who wheeze when exposed to a variety of triggers rather than solely with viral infections.[11] Identification of these patterns of wheeze might allow the clinician to classify children during an office visit.[11] However, the classifications of episodic and multiple-trigger wheeze might be unstable over time, with more than half of children classified into either episodic or multiple-trigger wheezing phenotypes switching to the other phenotype over the course of a year.[13]

Various models or clinical indicators of subsequent asthma risk have been studied to help the clinician identify those children who will continue wheezing into older childhood.[14-16] These models have included risk factors associated with the development of asthma in epidemiologic studies, such as parental history of allergic sensitization, wheezing history, atopic disease in the child, IgE levels, and cytokine secretion profiles.[14-16] An Asthma Predictive Index (API) to define future childhood asthma risk in young children was derived from the Tucson cohort data and includes risk factors, such as frequent wheezing, parental history of asthma, and signs of personal atopy (Table I).[14,17] A positive loose index result was defined as any parental report of wheezing on the surveys at 2 or 3 years of age and either 1 major criterion or 2 minor criteria. A positive stringent index result was defined as frequent wheezing on these same surveys (score of ≥3; scale = 1-5, from "very rarely" to "on most days") plus the same combination of major or minor criteria. Children with a positive loose index result were 4 times more likely than children with a negative loose index result to have active asthma during a subsequent survey at 6, 8, 11, or 13 years of age (sensitivity, 42%; specificity, 85%; likelihood ratio, 2.8). Children with a positive stringent index result were 7 times more likely than children with a negative stringent index result to have active asthma in at least 1 of these school-aged surveys (sensitivity, 16%; specificity, 97%; likelihood ratio, 5.3).

The API has recently been corroborated in the Leicester population-based birth cohort of 1954 children.[18] The API score and wheeze frequency were evaluated in 1954 children at 3 years of age and then compared with rates of asthma at 7 and 10 years of age. Results were comparable with the findings in the Tucson cohort, with a 5-fold increased risk of asthma at 7 years of age with a positive loose API result and an 8-fold increased risk with a positive stringent API result. Using a simpler rule of early wheeze (wheezing in the first 3 years of life) or early frequent wheeze produced similar results. Thus using the simpler definition might save screening costs. However, the authors concluded that the overall predictive performance for all measures was low, and these tests are imperfect at identifying children at risk of asthma. However, these tests have high negative predictive values, enabling the identification of children who are at low risk of later asthma when the API result is negative[19,20] and those in whom prolonged therapy might not be useful.

Other asthma risk scores have also been developed.[15,21,22] By using these scoring systems, combinations of risk factors, including recurrent chest infections at 2 years of age, a family history of asthma, a positive skin prick test response to at least 1 food or inhalant allergen at 4 years of age, recurrent nasal symptoms at 1 year of age,[21] greater severity of obstructive airway disease during the first 2 years of life,[15] male sex, postterm delivery, medium/low parental education, wheezing frequency, wheezing/dyspnea apart from colds, parental report of serious infections, and presence of doctor-diagnosed eczema,[22] confer significantly greater risk for a preschooler with wheeze to have persistent asthma in later childhood.

The API has recently been modified by replacing the clinical diagnosis of allergic rhinitis with evidence for allergic sensitization. This modified Asthma Predictive Index (mAPI; Table I) has been described and endorsed by the Expert Panel Report 3 (EPR3)[14,23,24] and although it is not prospectively validated, it might be a useful tool in identifying children who are more likely to have persistent wheezing and who might respond to inhaled corticosteroids (ICSs).[24] The sensitivity and specificity of the mAPI have yet to be determined.

HISTORY

A history of recurrent cough, wheeze, difficulty breathing, and chest tightness, particularly with exposure to classic asthma triggers, such as viral infections, exercise, allergens, or irritants, such as tobacco smoke, increases the probability that a child has asthma.[23] Eczema, hay fever, and/or a family history of asthma or atopic disease are often associated with asthma.[23]

The typical wheezing pattern in infants and preschool-aged children consists of short but recurrent exacerbations of cough and wheeze of varying severity and duration, usually triggered by viral upper respiratory tract illnesses and separated by long symptom-free intervals.[12] It is important to obtain a history regarding the following: timing and pattern of wheezing, either acute or chronic; associated factors, such as the relationship of these episodes to viral illness and feeding and past medical

TABLE I. mAPI* versus original API[14]

1. A history of ≥4 wheezing episodes with ≥1 physician's diagnosis.
2. In addition, the child must meet ≥1 of the following major criteria or ≥2 of the following minor criteria:

mAPI: major criteria
- Parental history of asthma
- Doctor-diagnosed atopic dermatitis
- **Allergic sensitization to ≥1 aeroallergen**

mAPI: minor criteria
- **Allergic sensitization to milk, egg, or peanut**
- Wheezing unrelated to colds
- Blood eosinophils ≥4%

Original API: major criteria
- Parental history of asthma
- Doctor-diagnosed atopic dermatitis

Original API: minor criteria
- **Doctor-diagnosed allergic rhinitis**
- Wheezing unrelated to colds
- Blood eosinophils ≥4%

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*Differences in indices are shown in boldface.

TABLE II. Age-related differential diagnosis for wheezing

Condition	Relative frequency of occurrence		
	Infancy	Childhood	Adolescence
Asthma	+	+++	+++
Airway malacia	++	+	−
Cystic fibrosis	+++	+	±
Foreign body	++	+++	±
Airway infection	+++	++	+
Bronchopulmonary dysplasia	+++	+	−
Primary ciliary dyskinesia	+	++	+
Bronchiectasis	+	+	+
Congenital anomalies (vascular ring)	+++	+	−
Vocal cord dysfunction	−	±	++
Tumors	±	±	±
Aspiration syndromes	+	±	±
Pulmonary edema	+	+	+

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−, Unlikely to present in this age group; +, likely to present in this age group.

history of comorbid conditions; response to previous treatments; family history of atopic disease; personal atopic history; and social and environmental factors that appear to contribute to morbidity.

The differential diagnosis of wheezing in childhood is complex and age dependent (Table II).[25] Features of atypical wheezing that should alert the physician to consider a diagnosis other than asthma should include the following: symptoms starting at or shortly after birth, continuous wheezing, failure to thrive, complete failure to respond to antiasthma medications, and no association with typical triggers, such as viral upper respiratory infections or exposure to allergens after sensitization to them. Wheezing during infancy and the preschool years might be the result of anatomic anomalies, such as airway malacia (tracheomalacia, bronchomalacia, or both), which is often accompanied by persistent noisy respirations and might be associated with a poor response to bronchodilators, corticosteroids, or both. Wheezing can result from extrinsic impingement of the airway by vascular (vascular ring/sling) or other thoracic (bronchogenic cyst, tumor, lymphadenopathy, and cardiomegaly) structures. Lesions within the airway can produce wheezing, such as laryngeal and tracheal webs.

Gastroesophageal reflux disease (GERD) is common in infancy and might be associated with chronic or recurrent respiratory tract symptoms, including wheezing,[26,27] although there remains uncertainty as to whether symptomatic gastroesophageal reflux is actually causative of wheezing in childhood or represents the unrelated coexistence of 2 relatively common problems (wheezing and GERD).[27] It has been estimated that as many as 45% to 65% of children with asthma have GERD.[28] However, a recent trial in school-aged children with poorly controlled asthma using ICSs without symptoms of GERD demonstrated that treatment with proton-pump inhibitors compared with placebo improved neither symptoms nor lung function but was associated with increased respiratory tract infections,[29] with similar findings among the group of children (43%) with evidence of GERD on pH probe testing.

Aspiration can produce airway obstruction and wheezing, as occurs after acute aspiration of a foreign body or chronic aspiration caused by a tracheoesophageal fistula or direct aspiration of oral or gastric secretions. More than 90% of acute foreign body aspiration events have an acute choking episode followed by coughing, wheezing, and/or stridor, whereas up to 10% of children with aspiration events have negative or doubtful histories.[30] Cystic fibrosis often presents with recurrent cough and wheeze that is frequently accompanied by loose greasy stools and poor weight gain. Primary ciliary dyskinesia can present with a history of recurrent cough and wheeze and chronic purulent otitis media. Congestive heart failure can produce "cardiogenic wheezing." Among infants born prematurely, especially those with very low birth weight, prolonged mechanical ventilation, or supplemental oxygen supplementation, chronic lung disease of prematurity or bronchopulmonary dysplasia should be considered, which can be accompanied by airway hyperreactivity and might predispose the patient to a subsequent asthma diagnosis.[31]

PHYSICAL EXAMINATION

A complete examination for asthma must be focused on both the upper and lower respiratory tracts, chest, and skin. Physical findings that increase the probability of asthma are hyperexpansion of the thorax (use of accessory muscles, appearance of hunched shoulders, and barrel configuration to the chest indicating chronic air trapping), sounds of wheezing during normal breathing or forced expiration, evidence of chronic rhinitis (infraorbital "shiners" and transverse nasal crease), and atopic dermatitis.[23] Unilateral wheezing might indicate foreign body aspiration or development of a pneumothorax. Sinusitis is uncommon in preschool-aged children but should be considered if the child has typical symptoms of prolonged purulent nasal discharge or malodorous breath because it might be contributory to instability of lower airway symptoms.[32] Poor growth is often an ominous sign of other diseases, such as congenital heart disease, cystic fibrosis, or immunodeficiency. Extremities should be examined for clubbing and cyanosis that could be associated with cystic fibrosis or other chronic lung or cardiac diseases. Neurologic examination should include signs of microcephaly or evidence of weakness that might lead to inadequate cough and aspiration leading to wheezing.

RADIOGRAPHIC AND LABORATORY STUDIES

First-tier evaluation of the child with recurrent wheeze should include a chest radiograph to evaluate for infiltrates, masses, great vessel abnormalities, radio-opaque retained foreign bodies, and signs of asymmetry. Posterior-anterior and lateral chest radiographs are usually indicated in the initial evaluation of a child with asthma, particularly if none have been performed previously. Peribronchiolar inflammatory changes and atelectasis are commonly observed in children with persistent asthma. Chest computed tomography allows for detection of thoracic masses, adenopathy, and bronchiectasis and definition of vascular structures. In older children with asthma, computed tomography might show several structural changes related to small-airway disease, including cylindrical bronchiolectasis, bronchial wall thickening, and air trapping, an indirect marker for bronchiolar obstruction.[33,34]

Sensitization to either indoor (dust mites, cockroaches, pets, and molds) or outdoor (pollens and molds) allergens is a major contributor to both chronic airway inflammation and acute asthmatic symptoms and should be considered when evaluating children for recurrent wheezing and asthma.[7,23]

Pulmonary function testing is helpful in the evaluation of wheezing, but spirometry is often not technically attainable in children younger than 4 to 5 years of age. If obtained, documenting at least partially reversible airflow obstruction (increase in FEV_1 of >12% from baseline or an increase >10% of predicted FEV_1 after inhalation of a short-acting β-agonist [SABA]) is helpful in establishing a diagnosis of asthma.[23] It should also be noted that FEV_1 is generally normal in children with asthma,[35] even those with severe persistent childhood asthma,[23] whereas the FEV_1/forced vital capacity ratio decreases as asthma severity increases.[36]

Although the majority of children with asthma can receive a diagnosis and be managed with the testing previously discussed, other laboratory tests might be informative as well. The presence of peripheral blood eosinophilia or an increased total serum IgE level is supportive but not diagnostic of asthma[32]; however, the absence of these findings does not rule out the diagnosis of asthma. Other tests might be helpful in selected situations, particularly in those children with recurrent pneumonias, failure to thrive, an atypical pattern of symptoms, or poor response to usual asthma therapy. Evaluation of immune competence might disclose an immune deficiency that predisposes the child to recurrent infections. Sweat chloride testing, a biopsy to evaluate ciliary ultrastructure and function, and bronchoscopy with bronchoalveolar lavage to evaluate pulmonary anatomy and infection are important in diagnosing other chronic respiratory diseases. An intermediate-strength purified protein derivative test (5 TU PPD) is important if tuberculosis is a diagnostic possibility.

MANAGEMENT OF EARLY ASTHMA IN CHILDREN: GOALS OF TREATMENT

The focus of asthma management over the past decade has become the attainment and maintenance of asthma control, which encompasses minimization of signs of both asthma impairment (daytime, nighttime, and exertional symptoms and/or rescue medication use) and risk (exacerbations, decrease in pulmonary function, and treatment-related adverse effects). This construct involves 2 major outcomes of interest: day-to-day symptom control (ie, impairment) and prevention of exacerbations. The preschool asthma population tends to be characterized as exacerbation prone with relatively limited impairment. Thus evidence obtained from populations of older children and adolescents who have more impairment-dominant disease might not be applicable in the majority of the preschool-aged group. Fortunately, recent evidence helps the practitioner evaluate the relative strengths and limitations of available treatment strategies.

Because asthma clearly has its origins in the preschool-aged group, the concept that early intervention in at-risk children might be effective in preventing subsequent asthma has received substantial attention recently. Unfortunately, several randomized, placebo-controlled clinical trials examining the role of ICSs in altering the natural history of asthma yielded negative findings.[24,37,38] However, 2 of the trials demonstrated that during the time when daily ICS therapy was used, there were indications of significant reductions in asthma-related morbidity, exacerbations, or both.[24,37]

CHALLENGES IN THERAPEUTIC DECISION MAKING IN THE PRESCHOOL-AGED GROUP

As mentioned previously, evaluation of therapeutic strategies in preschool-aged children with asthma-like symptoms is complex and largely related to the multiple phenotypes of wheezing in early life. The heterogeneity in wheezing patterns likely relates to differences in underlying pathophysiologic mechanisms causing wheezing, with resultant differences in response to medications. Some wheezing phenotypes appear to be mild and self-limited (eg, transient early wheezing) and thus might be most amenable to treatment for acute symptoms, whereas other phenotypes might result in greater impairment, risk, or both and deserve consideration for therapy aimed at minimizing or preventing these events. These multiple sources of disease heterogeneity have resulted in difficulty in designing and interpreting clinical trials in this age group. Several studies have included children with multiple wheezing phenotypes within the same trial, which might have resulted in negative findings for the population as a whole but positive findings within specific phenotypes. Recently, investigators have begun to focus on specific wheezing phenotypes in trial design, providing substantial insight into disease pathogenesis and management.

STEPWISE APPROACH TO ASTHMA MANAGEMENT

The National Asthma Education and Prevention Program (NAEPP)/EPR3 proposes a stepwise approach toward asthma management in all patients with asthma with the goal of achieving asthma control and has a specific approach for children 0 to 4 years of age (Fig 1).[23] Fundamental to the NAEPP/ERP3 treatment paradigm is the categorization of children as having either intermittent or persistent disease. The European Respiratory Society (ERS) Task Force has also developed guidelines for the treatment of wheezing children less than 6 years of age,[11] as has the Global Initiative for Asthma for children 5 years and younger.[39] These 3 sets of guidelines have taken different approaches toward disease classification and treatment. The NAEPP/EPR3 and Global Initiative for Asthma guidelines both focus on achieving asthma control through stepwise care approaches, whereas the ERS Task Force approach centers on the distinction between episodic (viral) wheeze and multitrigger wheezing. However, since all of these guidelines were last published, several well-conducted studies in this population warrant additional consideration and might now allow for treatment decisions to be made by

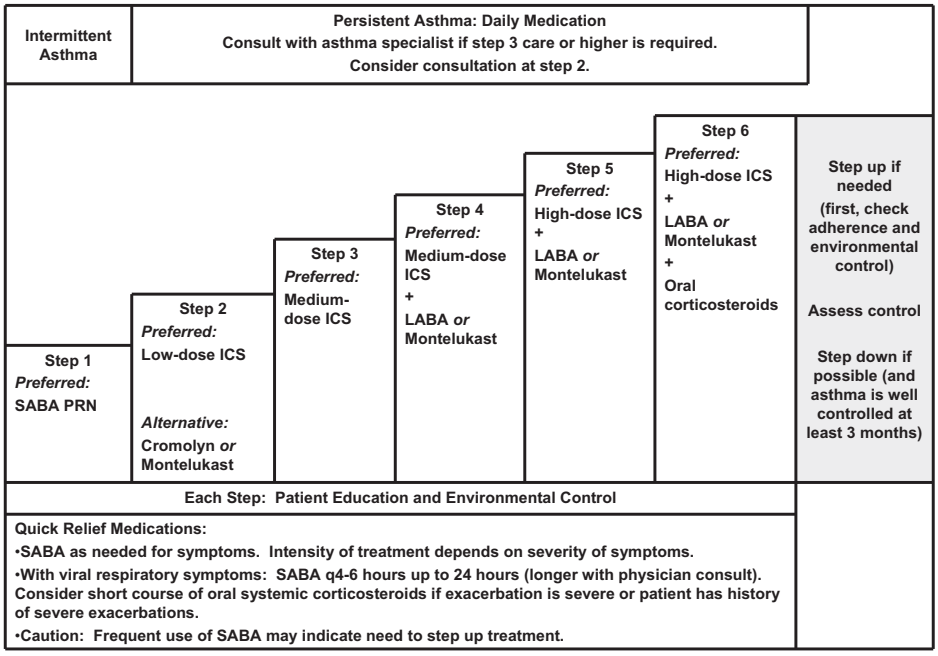

FIG 1. Stepwise approach for the long-term management of asthma in children 0 to 4 years of age. *LABA,* Long-acting β-agonist; *PRN,* as necessary; *q,* every. Modified from National Asthma Education and Prevention Program, Expert Panel Report III.[23]

incorporating both the level of asthma severity and other phenotypic characteristics (Fig 2).

MANAGEMENT OF INTERMITTENT DISEASE

Many preschool-aged children experience substantial asthma symptoms during acute respiratory tract illnesses but remain minimally symptomatic between episodes and have been referred to as having severe intermittent asthma[12] or episodic viral wheeze.[11] This pattern has led to the study of 2 general treatment strategies: daily therapy to prevent episodes and intermittent therapy provided on during (or just preceding) episodes.

Daily therapy

Despite the intermittent nature of this disorder, the frequency and severity of the associated wheezing episodes have prompted investigation focused on episode prevention by using daily controller therapy akin to that which is effective in older children with persistent asthma. Daily therapy for 2 years with ICSs has been demonstrated to reduce exacerbations and days with asthma symptoms among 2- to 3-year-old children with asthma risk factors (positive mAPI result) but without persistent asthma symptoms at study entry[24] but was associated with a negative effect on linear growth of 1.1 cm over the treatment period. A subgroup analysis demonstrated that among this relatively homogeneous cohort of preschool children with positive mAPI results, the response to ICSs was not uniform, and certain characteristics were associated with significantly greater positive effects from ICS therapy (male sex, white race, previous-year emergency department visit or hospitalization, and greater symptom burden at baseline).[40] A recent meta-analysis in preschoolers with recurrent wheezing and asthma found that daily ICS therapy was associated with a nearly 40% reduction in exacerbations along with lower symptom scores and less rescue albuterol use,[41] although the effect on exacerbations was most evident among children with a clinical diagnosis of asthma rather than recurrent wheezing not diagnosed as asthma.

Daily administration of the leukotriene receptor antagonist (LTRA) montelukast has been demonstrated to reduce the rate of asthma exacerbations by 31.9% compared with placebo among children 2 to 5 years of age with intermittent asthma.[42] However, no significant effect was noted in oral corticosteroid use, suggesting the effect of montelukast in this situation was on the attenuation of the less severe episodes.

Although both daily ICS and LTRA therapies have shown efficacy in the management of intermittent wheezing in preschool children, there are presently no direct comparative trials to help determine the relative efficacies of these approaches in this population with intermittent disease.

Intermittent therapy

Given the episodic nature of this condition, evaluation of therapeutic strategies involving intermittent medication administration has been the subject of several recent studies. Five recent trials have examined intermittent ICS therapy in children with intermittent wheeze, generally in the context of acute respiratory tract infections.

Bisgaard et al[38] found that administration of 400 μg of budesonide daily beginning 3 days after onset of respiratory tract symptoms did not alter the number or duration of asthma episodes compared with placebo.

Bacharier et al[43] found that use of either 1 mg of budesonide twice daily or 4 mg of montelukast once daily for 7 days in 1- to 5-year-old children with recurrent wheezing, when started at the early signs of a developing respiratory tract illness, did not reduce episode-free days or oral corticosteroid use during episodes over a 1-year period compared with placebo. However, among children with asthma risk factors (a positive mAPI result), both approaches resulted in modest symptom reduction during episodes.

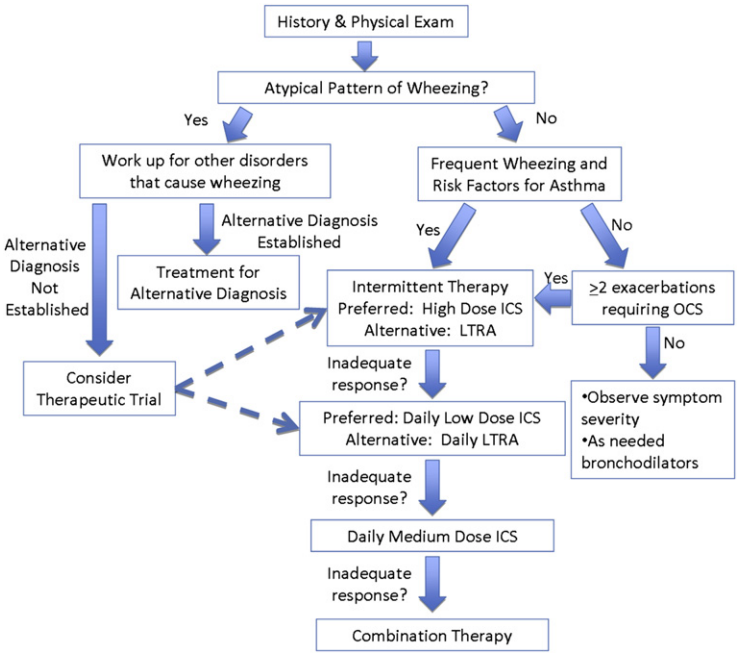

FIG 2. Proposed algorithm for the diagnosis and management of early childhood asthma. *OCS,* Oral corticosteroids.

Ducharme et al[44] administered 750 μg of fluticasone propionate twice daily or placebo to 1- to 6-year-old children with recurrent wheezing triggered by upper respiratory tract infections for up to 10 days, beginning at the onset of an upper respiratory tract infection. They noted a 50% reduction in the rate of exacerbations requiring oral corticosteroids, but enthusiasm for this approach was tempered by significantly smaller gains in height and weight.

Papi et al[45] treated children 1 to 4 years of age with frequent wheeze with either (1) twice-daily ICS (400 μg of beclomethasone) plus a SABA as needed for asthma symptoms, (2) daily placebo and an ICS plus SABA (800 μg of beclomethasone plus 1600 μg of salbutamol administered through a nebulizer) given as needed for symptoms, or (3) daily placebo and as-needed SABA (2500 μg administered through a nebulizer) for symptoms. Daily ICS therapy was superior to as-needed SABA alone in terms of the percentage of symptom-free days, but no difference was noted between daily and as-needed ICS therapy. Furthermore, the times to first exacerbation requiring oral corticosteroids did not differ between the daily ICS and as-needed ICS groups.

Most recently, Zeiger et al[46] compared daily ICS (0.5 mg of budesonide daily) with intermittent ICS (1 mg of budesonide twice daily at the early signs of a respiratory tract illness) in 278 children 12 to 53 months of age with recurrent severe wheezing and positive mAPI results. Over the 1-year trial, there were no significant differences between daily and intermittent therapy in terms of the rate of episodes requiring oral corticosteroids, episode severity, asthma symptom burden, or linear growth.

Episodic use of LTRA therapy has also been investigated in children with intermittent wheezing, with generally modest effects noted. In addition to the study noted above, Robertson et al[47] demonstrated that among children aged 2 to 14 years treated with montelukast or placebo at the onset of upper respiratory tract infection with symptoms and continued for a minimum of 7 days, the montelukast group experienced a 28.5% reduction in unscheduled health care resource use, and subgroup analysis suggested this effect was more evident in the 2- to 5-year-old participants. In addition, they noted clinically modest but statistically significant reductions in symptoms and time off work, school, or both.

Valovirta et al[48] compared episode-driven (12 days) montelukast started at signs/symptoms consistent with imminent cold or breathing problems with daily montelukast and placebo in children 6 months to 5 years of age with recurrent wheezing and asymptomatic periods between episodes. Neither daily nor episodic montelukast reduced the number of episodes requiring health resource use, whereas daily montelukast reduced symptoms during episodes compared with placebo, and both montelukast strategies reduced β-agonist use. The ERS Task Force report recommends episodic use of montelukast for the treatment of episodic (viral) wheeze.[11]

MANAGEMENT OF PERSISTENT DISEASE

The approach to the young child with features of persistent asthma, as defined by the NAEPP/EPR3 (Fig 1), includes the recommendation for long-term control therapy to reduce impairment and risk in children with recurrent wheezing (≥4 episodes in the past year lasting >1 day and affecting sleep) who have asthma risk factors defined as a positive API result (evidence level A).[23] These recommendations are based heavily on the results of the Preventing Early Asthma in Kids (PEAK) trial (described above) demonstrating reduced asthma morbidity during a 2-year period with low-dose ICS relative to placebo.[24] Furthermore, long-term control therapy aimed at reduction in impairment is appropriate and should be considered for children who consistently require symptomatic treatment for more than 2 days per week for a period of more than 4 weeks (evidence level D) and those who have experienced at least 2 exacerbations requiring oral corticosteroids within 6 months (evidence level D) and can be considered during periods (or seasons) of previously documented risk (evidence level D).[23] As noted by evidence level D,

these latter 3 considerations are based on expert opinion and extrapolation from studies in older children, as are all treatment recommendations beyond step 2 care in this age group (Fig 1).

Daily ICSs

Over the past decade, it has become evident that daily therapy with ICSs is effective in improving asthma control in the preschool-aged asthmatic population. Multiple trials have demonstrated the efficacy of several ICS preparations, including budesonide inhalation suspension,[49-51] fluticasone propionate metered-dose inhaler (MDI),[24,52-56] and ciclesonide MDI.[57] A recent systematic literature review[58] and meta-analysis[41] both concluded that maintenance therapy with ICSs is more effective than placebo in controlling asthma symptoms in preschool children, with the effect on exacerbations most evident among children with a clinical diagnosis of asthma rather than recurrent wheezing not diagnosed as asthma.[41] There were no significant differences in ICS effects based on atopic status, whether children were enrolled in a method of ICS delivery (MDI vs nebulizer), ICS product (budesonide vs fluticasone), or age, and it was determined that 7 children needed to be treated with daily ICSs to prevent 1 wheezing/asthma exacerbation.[41]

The clearly established clinical benefit provided by daily ICS therapy must be balanced against the potential risks associated with this approach in preschool children, with linear growth remaining the dominant concern. Although multiple studies in older children have consistently demonstrated a clinically modest but statistically significant effect in linear growth (typically approximately 1.1 cm over the first year of therapy), these findings should not be directly extrapolated to preschool children because linear growth in children less than 3 years of age is influenced by factors other than growth hormone (eg, nutrition).[59] This might explain why trials in preschool-aged children have demonstrated either similar growth effects[24,60] or no statistically significant effects of ICS therapy[49,51,54] on growth velocity. Furthermore, the long-term implications of a slowing of growth velocity are unclear and might be age and weight dependent. Guilbert et al[61] reported that, in contrast to the 1.1-cm difference in growth during 2 years of treatment with 88 μg of fluticasone propionate twice daily, 2 years after discontinuation of ICSs, there was no longer a significant difference overall in linear growth relative to that seen in placebo-treated children. However, those children who entered the trial at a younger age (2 years of age), weighed less than 15 kg, and were treated with ICSs during the trial continued to have less linear growth (1.9 cm) 2 years after stopping ICS therapy than children treated with placebo, potentially a result of higher relative exposure to ICSs. These findings highlight that the growth-suppressive effects of ICS therapy in preschool children in general are small, on average, and appear to improve over time in most children, but there remain subgroups of children who might experience greater than expected effects on linear growth; the long-term consequences of these findings are not known. Overall, the literature supports the conclusion that long-term use of low-dose ICS therapy is well tolerated with clinically modest effects on linear growth, but data are limited in terms of the long-term growth effects of moderate- to high-dose ICS therapy. Regardless of ICS dosing, regular monitoring of growth in children receiving ICS therapy remains appropriate, with continued attempts to titrate the ICS dosing to the minimally effective dose. Furthermore, Amirav et al[62] recently highlighted the multitude of factors that affect efficacy and that might affect the safety of ICSs in young children, including anatomic and emotional factors, along with differences in airway physiology and aerosol delivery.

It is important to note that, in general and among preschool-aged children in particular, there is a limited clinically relevant dose-response relationship demonstrable for ICS therapy. The pivotal trials for budesonide nebulization suspension did not demonstrate significant differences in either impairment or risk domain outcomes between low-dose budesonide (0.25 mg twice daily) and higher-dose budesonide (1 mg twice daily).[63] A trial with fluticasone propionate (100 μg/d vs 200 μg/d) demonstrated a modest dose-dependent effect on exacerbations, with the 200 μg/d group experiencing a significant reduction in exacerbations relative to placebo, whereas there was no reduction in exacerbations among the low-dose group relative to placebo.[55] There were no significant differences between the 2 doses in terms of asthma symptoms and rescue albuterol use. Brand et al[57] recently demonstrated the absence of a dose-response relationship in severe exacerbations between 3 doses of ciclesonide (40, 80, and 160 μg once daily). However, recognizing the challenges associated with drug delivery in this population, the NAEPP/EPR3 guidelines recommend medium-dose ICS therapy in patients whose symptoms are not controlled with low-dose ICS therapy to ensure that an adequate dose of ICS is being delivered to the lower airways before consideration of adjunctive therapy.[23]

Daily LTRAs

Clinical trial data in preschool-aged children with persistent asthma demonstrate that daily use of montelukast for 12 weeks significantly reduces asthma symptom frequency, rescue albuterol use, oral corticosteroid use, and peripheral blood eosinophil counts.[64] Unlike the findings for subgroups of children with greater responses to daily ICS therapy,[40] specific characteristics, including markers of atopic disposition, did not identify subgroups of children who derived the greatest benefit from montelukast.[65] Among 26 preschool-aged children with mild asthma, montelukast therapy over a 4-week period was associated with a 2.5-fold reduction in bronchial hyperresponsiveness (BHR) to methacholine relative to placebo.[66] Initiation of open-label montelukast in preschool-aged children with persistent asthma and fraction of exhaled nitric oxide levels of 10 ppb or greater was associated with a significant decrease in fraction of exhaled nitric oxide levels, along with improvements in BHR to adenosine, lung function (by means of forced oscillation), and symptom scores over an 8-week period.[67] Finally, in recognition that the risk of asthma exacerbations increases significantly in September, a trial of the addition of montelukast or placebo to usual asthma therapy from September 1 to October 15 demonstrated significant reductions in days with worse asthma symptoms (53% less) and unscheduled physician's office visits (78% less) among the montelukast group.[68] In contrast, Weiss et al[69] did not demonstrate an improvement when montelukast was added to standard therapy just before return to school in children 6 to 14 years of age. The overall safety experience with montelukast in pediatric patients has been excellent, with the most commonly reported side effects being upper respiratory tract infection, worsening asthma, pharyngitis, and fever.[70] Neuropsychiatric events have been reported infrequently in patients of all ages taking montelukast, although preschool-aged children do not appear to be more susceptible to such effects than older subjects.[71]

The NAEPP/EPR3 guidelines identify ICSs as the preferred controller at step 2, with montelukast identified as an alternative in children 0 to 4 years of age, a recommendation supported by 2

comparative trials. Szefler et al[72] reported an open-label trial of children 2 to 8 years of age with mild persistent asthma or recurrent wheezing and active asthma symptoms, which randomized participants to receive either 0.5 mg of budesonide inhalation suspension once daily or 4 or 5 mg of montelukast once daily for 52 weeks. There was no significant difference in the time to first additional asthma medication at 52 weeks between the treatment groups, although the budesonide group experienced a significant 25% lower rate of exacerbations and a numerically but not statistically significant reduction in oral corticosteroid use.

Kooi et al[73] conducted a placebo-controlled randomized trial in 63 children 2 to 6 years of age with asthma-like symptoms on 2 or more days per week during a 2-week run-in period. Children received either 4 mg of montelukast daily or 100 μg of fluticasone twice daily through an MDI and valved holding chamber or placebo for 3 months. All 3 groups experienced symptom improvement relative to baseline, but when compared with the placebo group, only the fluticasone group experienced a significant reduction in daily symptom scores. The montelukast group experienced a significant reduction in peripheral blood eosinophil counts. Neither active group experienced a significant change in lung function relative to placebo.

Combination ICS/long-acting β-agonist

Among children 0 to 4 years of age with persistent asthma that is not controlled with daily moderate-dose ICS therapy, the current NAEPP/EPR3 guidelines suggest initiation of combination controller therapy consisting of medium-dose ICS plus either a long-acting β-agonist (LABA) or montelukast. These recommendations are based on extrapolation from studies in older children and adults because there are no published prospective randomized controlled studies comparing such approaches in children 0 to 4 years of age. Sekhsaria et al[74] retrospectively evaluated 50 children 5 to 60 months of age with recurrent wheezing who were receiving open-label combination therapy with low- to medium-dose fluticasone (88-440 μg/d) plus salmeterol (using separate chlorofluorocarbon-based MDIs with valved holding chambers with facemasks) for at least 3 months. Compared with historical disease activity before ICS plus LABA therapy, use of combination therapy was accompanied by statistically significant reductions in wheezing frequency and health care use (ED visits and hospitalizations). However, the substantial methodologic limitations of this study preclude using findings from this trial alone to support the efficacy of ICS plus LABA in this age group. The lack of prospective controlled trials of ICS plus LABA and ICS plus LTRA therapy in this age group presents the clinician with a challenging situation when faced with a young child with persistent and uncontrolled asthma despite ICS therapy. Future properly designed trials will be essential in determining what role combination ICS plus LABA therapy plays in this age group.

SUMMARY

The heterogeneity of early childhood wheezing and asthma explains many of the clinical challenges inherent in the care of the preschool child with recurrent wheeze. Fortunately, recent research has provided several useful constructs that subdivide wheezing into phenotypes with differing prognoses and potentially different response patterns to available treatment strategies. Future investigations in early childhood asthma should include clearly defining the wheezing phenotype or phenotypes to be studied *a priori*. Furthermore, exploration of other (and hopefully better) predictors of disease course, including genetic markers, might allow for more targeted therapeutic approaches both in terms of the appropriate patient population and the pharmacologic or environmental target.

What do we know?

- **Early childhood wheezing and asthma are heterogeneous disorders with many phenotypic and variable expressions during childhood.**
- **The typical wheezing pattern in infants and preschool-aged children consists of short but recurrent exacerbations of cough and wheeze triggered by viral infections and separated by long symptom-free intervals.**
- **Documenting at least partially reversible airflow obstruction on lung function, allergen sensitization, increased IgE levels, or blood eosinophilia, if present, is helpful in establishing a diagnosis of asthma. However, the evaluation of asthma in very young children is further complicated by the lack of objective lung function measurements and definitive biomarkers.**
- **The preschool-aged asthmatic population tends to be characterized as exacerbation prone with relatively limited impairment. There are data to support the use of daily and intermittent controller therapies in this population.**
- **The management of the young child with persistent asthma is based largely on expert opinion and extrapolation from studies in older children given the relative lack of high-quality trials in this age group.**

What is still unknown?

- **There is not a definitive biomarker to identify children with high-risk phenotypes who will go on to have persistent asthma.**
- **It is not clear how to manage asthma in the different phenotypes, particularly children with nonatopic wheezing.**
- **An effective primary or secondary asthma-prevention strategy has not been identified.**
- **Both daily ICS and LTRA therapies have shown efficacy in the management of intermittent wheezing in preschool children, and intermittent high-dose ICS therapy is comparable in efficacy to daily low-dose ICS therapy in high-risk children.**
- **Treatment recommendations beyond step 2 care require properly designed trials to determine what role combination therapies play in this age group.**
- **In the preschool-aged group there is a limited, clinically relevant dose-response relationship demonstrable for low-dose ICS therapy, and data are limited in terms of the long-term growth effects of moderate- to high-dose ICS therapy.**
- **There is little known regarding how the anatomic differences and lower inspiratory flow rate affect medication deposition in young children by using the current drug delivery devices and spacers available.**

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